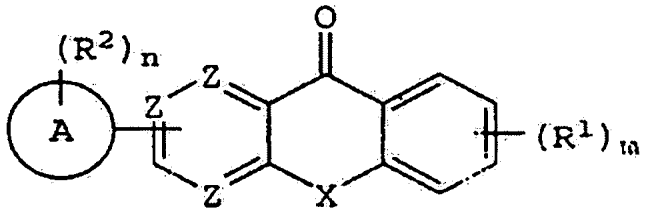
In the Claims

Please replace all prior versions, and listings, of claims in the application with the following list of claims:

Applicant has submitted a complete claim set in which insertions indicated by underlining and strikeouts and/or double bracketing, respectively.

1. (Original) A DNA-PK inhibitor having a formula



or a pharmaceutically acceptable salt thereof,

wherein m is an integer 0 through 3;

n is an integer 0 through 4;

X is O, $S(O)_{0-2}$, or NR^a;

Z, independently, is CR^b or N;

A is heteroaryl or a four- to seven-membered aliphatic ring containing 0, 1, 2, or 3 heteroatoms independently selected from the group consisting of N, O, and S;

R^1, independently, is selected from the group consisting of halo, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, $N(R^d)_2$, OR^d, carboxyl, carboxy, nitro, OC_{1-3}alkyleneN$(R^d)_2$, N(R^d)-C_{1-3}alkyieneN$(R^d)_2$, OC_{1-3}alkyleneC(=O)OR^d, O(C_{1-3}alkylene) OP(=O)$(OR^d)_2$, O(C_{1-3}alkylene)OP(=O)$(ONa)_2$,OP(=O)-$(OR^d)_2$, OP(=O)$(ONa)_2$, cyano, aldehyde, carboxamide, thiocarboxamide, acyl, mercapto, sulfonyl, trifluoromethyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; or

two R^1 groups are taken together with the atoms to which each is attached to form a 5-, 6-, or 7-membered ring, wherein 1 or 2 carbon atoms of R^1 optionally is a heteroatom

selected from the group consisting of O, N, and S, said ring optionally substituted with one or more =O, =S, =NH, OR^c, $N(R^d)_2$, carboxyl, carboxy, alkyl, aryl, substituted aryl, heteroaryl, or substituted hetercaryl, said heteroatom optionally substituted with a group selected from the group consisting of aryl, substituted aryl, alkyl, substituted alkyl, and acyl;

R^2, independently, is selected from the group consisting of OR^d, halo, $N(R^d)_2$, aldehyde, alkyl, substituted alkyl, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl,
C_{1-3}alkyleneOR^d, C (=O)N$(R^d)_2$, N$(R^d)_2$, (C=O)OR^d, NO_2 ,NR^{d}C (=O)R^d, NR^d(SO_2)R^d, OC_{1-3}alkyleneOR^d, OC_{1-3}alkyleneOC_{1-3}alkyleneR^d, OC(=O)R^d, OC_{1-3}alkyleneC(=O)C_{1-3}alkyleneR^d, and (SO_3) R^d;

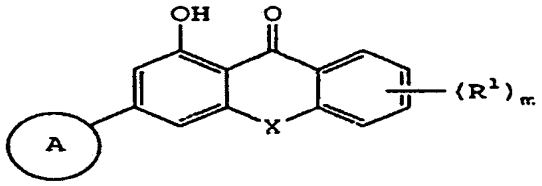
R^a is selected from the group consisting of hydro, C_{1-4}alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, C_{1-3}alkylenearyl, C_{1-3}alkyleneheteroaryl, C_{1-3}alkyleneheterocycloalkyl, C_{1-4}alkylene-N$(R^d)_2$, C_{1-4}alkyleneOR^d, C_{1-4}alkyleneC(=O)OR^d, C(=O)R^d, C(=O)N$(R^d)_2$, C(=O)OR^d, C(=O)SR^d, C(=S)N$(R^d)_2$,SO_2R^d, SO_2N$(R^d)_2$, C(=O)NR^dC_{1-4}alkyleneOR^d, C(=O)NR^dC_{1-4}alkyleneheterocycloalkyl, C(=O)C_{1-4}alkylenearyl, C(=O)C_{1-4}alkyleneheteroaryl, C_{1-4}alkyleneC (=O) C_{1-4}alkylenearyl,C_{1-4}alkyleneC (=O)C_{1-4}alkyleneheteroaryl, C_{1-4}alkylene-C(=O) heterocycloalkyl, C_{1-4}alkyleneNR^{d}C(=O)R^d, C_{1-4} alkyleneOC_{1-4}a1kyleneOR^d, C_{1-4}alkyleneOC_{1-4}alkyleneC(=O)OR^d, and C_{1-4}alkyleneC(=O)N$(R^d)_2$;

R^b, independently, is selected from the group consisting of hydro, alkyl, halo, aldehyde, OR^d, O(C_{1-3}alkylene)OP(=O)$(OR^d)_2$, O(C_{1-3}alkylene)OP(=O)$(ONa)_2$, OP(=O)$(OR^d)_2$, OP(=O)$(ONa)_2$, nitro, N$(R^d)_2$, carboxyl, carboxy, sulfonamido, sulfamyl, and sulfo or a halide derivative thereof; and

R^d, independently, is selected from the group consisting of hydro, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, aryl, C_{1-3}alkylenearyl, substituted aryl, heteroaryl, and substituted heteroaryl.

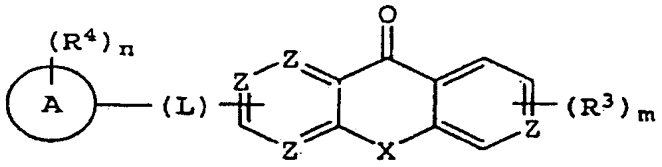
2-8. (Canceled)

9. (Original) The inhibitor of claim 1 having a structure



10. (Canceled)

11. (Original) A DNA-PK inhibitor having a formula:



or a pharmaceutically acceptable salt thereof,

wherein m is an integer 0 through 3;

n is an integer 0 through 4;

X is O or NR^a;

Z, independently, is CR^b or N;

L is selected from the group consisting of alkylene, substituted alkylene, carbonyl, carbamoyl, $-NR^d-$, $-N(R^d)_2$, $-O(SO_2)R^d$, $-SO_2R^d$, oxy (-O-), thio (-S-), thionyl (-SO-), and sulfonyl;

A is absent, or A is heteroaryl or a four-to seven-membered aliphatic ring containing 0, 1, 2, or 3 heteroatoms independently selected from the group consisting of N, O, and S;

R^1, independently, is selected from the group consisting of halo, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heterocycloalkyl, substituted heterocycloalkyl, $N(R^d)_2$, OR^d, carboxyl, carboxy, nitro, $OC_{1-3}alkyleneN(R^d)_2$, $N(R^d)_{1-3}alkyleneN(R^d)_2$, OC_{1-}

$_3$alkyleneC(=O)OR^d, O(C_{1-3}alkylene)OP(=O)(OR^d)$_2$, O(C_{1-3}alkylene)OP(=O)(ONa)$_2$, OP(=O)(OR^d)$_2$, OP(=O)(ONa)$_2$, cyano, aldehyde, carboxamide, thiocarboxamide, acyl, mercapto, sulfonyl, trifluoromethyl, aryl, substituted aryl, heteroaryl, and substituted heteroaryl; or

two R^1 groups are taken together with the atoms to which each is attached to form a 5-, 6-,or 7-membered ring, wherein 1 or 2 carbon atoms of R^1 optionally is a heteroatom selected from the group consisting of O, N, and S, said ring optionally substituted with one or more of =O, =S, =NH, OR^c, N(R^d)$_2$, carboxyl, carboxy, alkyl, aryl, substituted aryl, heteroaryl, or substituted heteroaryl, and said heteroaryl optionally substituted with a substituent selected from the group consisting of aryl, substituted aryl, alkyl, substituted alkyl, and acyl;

R^2, independently, is selected from the group consisting of OR^d, halo, N(R^d)$_2$, aldehyde, alkyl, substituted alkyl, acyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl C_{1-3}alkyleneOR^d, C(=O)N(R^d)$_2$, N(R^d)$_2$, (C=O)OR^d, NO_2, NR^{d}C(=O)R^d, NR^d(SO_2)R^d, OC_{1-3}alkyleneOR^d, OC_{1-3}alkyleneOC_{1-3}alkyleneR^d, OC(=O)R^d, OC_{1-3}alkyleneC(=O)C_{1-3}alkyleneR^d, and(SO_3)R^d;

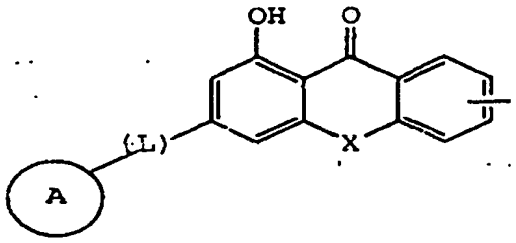
R^a is selected from the group consisting of hydro, C_{1-4}alkyl, aryl, heteroaryl, cycloalkyl, heterocycloalkyl, C_{1-3}alkylenearyl, C_{1-3}alkyleneheteroaryl,C_{1-3}alkyleneheterocycloalkyl, C_{1-4}alkylene-N(R^d)$_2$, C_{1-4}alkyleneOR^d; C_{1-4}alkyleneC(=O)OR^d, C(=O)R^d, C(=O)N(R^d)$_2$, C(=O)OR^d, C(=O)SR^d, C(=S)N(R^d)$_2$, SO_2R^d, SO_2N(R^d)$_2$, C(=O)NR^dC_{1-4}alkyleneOR^d, C(=O)NR^dC_{1-4}alkyleneheterocycloalkyl, C(=O)C_{1-4}alkylenearyl, C(=O)C_{1-4}alkyleneheteroaryl, C_{1-4}alkyleneC(=O)C_{1-4}alkylenearyl, C_{1-4}alkyleneC(=O)C_{1-4}alkyleneheteroaryl, C_{1-4}alkyleneC(=O)heterocycloalkyl, C_{1-4}alkyleneNR^{d}C(=O) R^d, C_{1-4}alkyleneOC_{1-4}alkyleneOR^d, C_{1-4}alkyleneOC_{1-4}alkylene-C(=O)OR^d, and C_{1-4}alkyleneC(=O)N(R^d)$_2$;

R^b, independently, is selected from the group consisting of hydro, alkyl, halo, aldehyde, OR^d, O(C_{1-3}alkylene)OP(=O)(OR^d)$_2$, O(C_{1-3}alkylene)OP(=O)(ONa)$_2$, OP(=O)(OR^d)$_2$, OP(=O)(ONa)$_2$, nitro, N(R^d)$_2$, carboxyl, carboxy, sulfonamido, sulfamyl, and sulfo or a halide derivative thereof; and

R^d, independently, is selected from the group consisting of hydro, alkyl, substituted alkyl, cycloalkyl, substituted cycloalkyl, heteroocycloalkyl, substituted heterocycloalkyl, aryl, C_{1-3}alkylenearyl, substituted aryl, heteroaryl, and substituted heteroaryl.

12-19. (Canceled)

20. (Original) The inhibitor-of claim 11 having a structure



and prodrugs thereof.

21. (Canceled)

22. (Original) A DNA-PK inhibitor selected from the group consisting of:
trifluoromethanesulfonic acid 1-hydroxy-9-oxo-9H-xanthen-3-yl ester;
1-hydroxy-3-morpholin-4-yl-xanthen-9-one;
1-hydroxy-6-methoxy-3-trifluoromethanesulfonylxanthen-9-one ester;
1-hydroxy-6-methoxy-3-morpholin-4-yl-xanthen-9-one;
6-fluoro-l-hydroxy-3-morpholin-4-yl-xanthen-o-one;
1-hydroxy-6-(4-methylpiperazin-1-yl)-3-morpholin-4-yl-xanthen-9-one;
1-(8-hydroxy-6-morpholin-4-yl-9-oxo-9H-xanthen-3-yl)-piperidine-4-carboxylic acid amide; trifluoromethanesulfonic acid 1-hydroxy-9-oxo-9,10-dihydro-acridin-3-yl ester; and 1-hydroxy-3-morpholin-4-y1-10H-acridi-9-one.

23. (Currently amended) A pharmaceutical composition comprising (a) DNA-PK inhibitor of claim 1 [[or claim 11,]] and (b) a pharmaceutically acceptable carrier or diluent.

24. (Currently amended) A pharmaceutical composition comprising (a) a DNA-PK inhibitor of claim 1 [[or 11,]] and (b) an antineoplastic agent.

25-29. (Canceled)

30. (Currently amended) A method of inhibiting DNA-PK activity comprising the step of contacting a DNA-PK with a DNA-PK inhibitor of claim 1 [[or 11]].

31. (Currently amended) A method of sensitizing a cell type to an agent that induces DNA lesions comprising the step of contacting the cell type with a compound of claim 1 [[or 11]].

32. (Canceled)

33. (Currently amended) A method of potentiating a therapeutic regimen for treatment of a cancer comprising the step of administering to an individual in need thereof an effective amount of a DNA-PK inhibitor of claim 1 [[or 11]].

34. (Canceled)

35. (Currently amended) A method of characterizing the potency of a test compound as an inhibitor of a DNA-PK polypeptide, said method comprising the steps of:

a) measuring an activity of a DNA-PK polypeptide in the presence of a test compound;

b) comparing the activity of the DNA-PK polypeptide in the presence of the test compound to the activity of the DNA-PK polypeptide in the presence of an equivalent amount of a reference compound of claim 1 [[or 11]], wherein a lower activity of the DNA-PK polypeptide in the presence of the test compound than in the presence of the reference compound indicates that the test compound is a more potent inhibitor than the reference compound, and a higher activity of the DNA-PK polypeptide in the presence of the test

compound than in the presence of the reference compound indicates that the test compound is a less potent inhibitor than the reference compound.

36. (Currently amended) A method of characterizing the potency of a test compound as an inhibitor of a DNA-PK polypeptide, said method comprising the steps of:

a) determining an amount of a control compound of claim 1 [[or 11]] that inhibits an activity of a DNA-PK polypeptide by a reference percentage of inhibition, thereby defining a reference inhibitory amount for the control compound;

b) determining an amount of a test compound that inhibits an activity of a DNA-PK polypeptide by a reference percentage of inhibition, thereby defining a reference inhibitory amount for the test compound;

c) comparing the reference inhibitory amount for the test compound to a reference inhibitory amount determined according to a step (a) for the control compound, wherein a lower reference inhibitory amount for the test compound than for the control compound indicates that the test compound is a more potent inhibitor than the control compound, and a higher reference inhibitory amount for the test compound than for the control compound indicates that the test compound is a less potent inhibitor than the control compound.

37-39. (Canceled)

40. (Currently amended) An article of manufacture comprising:

a) an anticancer compound that induces double-strand DNA breakage in cells; and

b) a package insert describing a coordinated administration to a patient of said anticancer compound and a DNA-PK inhibitor compound of claim 1 [[or 11]].

41-45. (Canceled)

46. (New) A pharmaceutical composition comprising (a) DNA-PK inhibitor of claim 11 and (b) a pharmaceutically acceptable carrier or diluent.

47. (New) A pharmaceutical composition comprising (a) a DNA-PK inhibitor of claim 11 and (b) an antineoplastic agent.

48. (New) A method of inhibiting DNA-PK activity comprising the step of contacting a DNA-PK with a DNA-PK inhibitor of claim 11.

49. (New) A method of sensitizing a cell type to an agent that induces DNA lesions comprising the step of contacting the cell type with a compound of claim 11.

50. (New) A method of potentiating a therapeutic regimen for treatment of a cancer comprising the step of administering to an individual in need thereof an effective amount of a DNA-PK inhibitor of claim 11.

51. (New) A method of characterizing the potency of a test compound as an inhibitor of a DNA-PK polypeptide, said method comprising the steps of:

a) measuring an activity of a DNA-PK polypeptide in the presence of a test compound;

b) comparing the activity of the DNA-PK polypeptide in the presence of the test compound to the activity of the DNA-PK polypeptide in the presence of an equivalent amount of a reference compound of claim 11, wherein a lower activity of the DNA-PK polypeptide in the presence of the test compound than in the presence of the reference compound indicates that the test compound is a more potent inhibitor than the reference compound, and a higher activity of the DNA-PK polypeptide in the presence of the test compound than in the presence of the reference compound indicates that the test compound is a less potent inhibitor than the reference compound.

52. (New) A method of characterizing the potency of a test compound as an inhibitor of a DNA-PK polypeptide, said method comprising the steps of:

a) determining an amount of a control compound of claim 11 that inhibits an activity of a DNA-PK polypeptide by a reference percentage of inhibition, thereby defining a reference inhibitory amount for the control compound;

b) determining an amount of a test compound that inhibits an activity of a DNA-PK polypeptide by a reference percentage of inhibition, thereby defining a reference inhibitory amount for the test compound;

c) comparing the reference inhibitory amount for the test compound to a reference inhibitory amount determined according to a step (a) for the control compound, wherein a lower reference inhibitory amount for the test compound than for the control compound indicates that the test compound is a more potent inhibitor than the control compound, and a higher reference inhibitory amount for the test compound than for the control compound indicates that the test compound is a less potent inhibitor than the control compound.

53. (New) An article of manufacture comprising:

a) an anticancer compound that induces double-strand DNA breakage in cells; and

b) a package insert describing a coordinated administration to a patient of said anticancer compound and a DNA-PK inhibitor compound of claim 11.